Homogeneously Catalyzed Formaldehyde Condensation to Carbohydrates

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Studies conducted in a continuous stirred tank reactor have produced quantitative results on the kinetics of the $Ca(OH)_2$ catalyzed formose reaction and its associated Cannizzaro effects. Combined feed molarities were varied from $5.60\ M$ HCHO and $1.034\ M\ Ca(OH)_2$ to one-tenth of these values. The observed autocatalytic and zero order nature of the kinetics of the homogeneously catalyzed formaldehyde condensation reaction were explained by using rate expressions which are analogous to Langmuir-Hinshelwood relationships. Product decomplexing is the rate limiting step, under the conditions studied. The rate of the formose condensation reaction at intermediate conversion levels at 60°C is, expressed as moles of HCHO converted/min/liter of reaction volume, $3.15 \times Ca(OH)_2$ molarity. The Cannizzaro reaction rate passes through a maximum near 50% conversion, then a minimum near 90%, and then sharply increases when reaction severity approaches 100% conversion. Terminal products determined by GLC analyses are 10% C_4, 30% C_5, 50% C_6, and 5% $> C_6$ carbohydrate species. Product distributions at intermediate conversion levels are provided.

INTRODUCTION

The formose reaction, or self-condensation of formaldehyde by alkaline catalysts to a complex carbohydrate mixture, was first reported by Butlerow (1) in 1861. Since that time there has been intermittent research on the reaction, primarily to identify and characterize various components of the product mixture. More recently, investigations have centered on increasing the selectivity of the reaction to lower molecular weight (C_2–C_4) compounds and their reduction to polyols. It is to this end and to a more fundamental and quantitative knowledge of the formose reaction that this research has been directed.

A study of formose chemistry can be broken down into four major divisions: the initial condensation reaction of formaldehyde with itself, later aldol-type condensa-
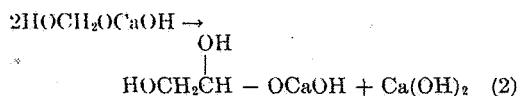
tions, the Cannizzaro reaction, and isomerization of the hydroxy aldehydes and ketones formed.

Glycolaldehyde (CH_2OHCHO) has been reported (2) to be the primary condensation product. Katschmann (3) accounts for the autocatalytic nature of the reaction by proposing that the primary condensation to glycolaldehyde is slow compared to later condensation reactions. Franzen and Hauck (4) isolated several metallic salts of formaldehyde and studied the possibility of their being an intermediate in the condensation of formaldehyde to sugars. They suggest a reaction of the type:

$$Ca(OH)_2 + 2CH_2(OH)_2 \rightleftharpoons Ca(OCH_2OH)_2 + 2H_2O, \quad (1)$$
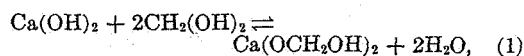
where methylene glycol, the major form of monomeric formaldehyde in aqueous solu-
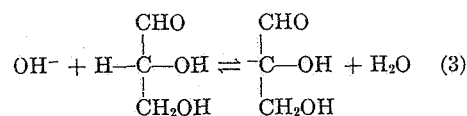
tion, is complexed by Ca(OH)$_2$. In very dilute solutions of formaldehyde they suggest formation of a salt of the type HOCH$_2$OCaOH. It is their conclusion that two salt molecules of this type condense to form complexed glycolaldehyde and Ca(OH)$_2$.

$$2\text{HOCH}_2\text{OCaOH} \rightarrow$$
$$\begin{array}{c} \text{OH} \\ | \\ \text{HOCH}_2\text{CH} - \text{OCaOH} + \text{Ca(OH)}_2 \quad (2) \end{array}$$
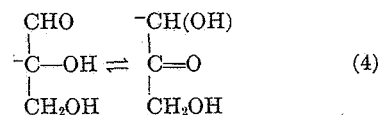
They also suggest that further condensations of this type lead to formose sugars. Balezin (5) similarly proposes that complexed Ca(OH)$_2$ plays an essential role in the condensation mechanism. Kuzin (6) has conducted experiments which indicate that saccharates of bivalent metals, e.g., calcium fructosate, are indeed the catalytic species for formaldehyde condensation. Kuzin also notes that polyols such as glycerol and mannitol have no catalytic influence. Other catalysts than Ca(OH)$_2$ are possible, and the reader is recommended to studies by Gutsche et al. (7) on pyridine bases and to work by Langenbeck (8) on benzoyl carbinols. Berl and Feazel (9) show that NaOH is a catalyst for glyceraldehyde condensation, and Pfeil and Schroth (10) provide results on formaldehyde condensation with dihydroxyacetone cocatalyst using other monovalent bases, such as LiOH and TlOH. Divalent bases are evidently not a prerequisite for the formose reaction to proceed. Breslow (11) notes that TlOH is a good catalyst for formaldehyde in the absence of cocatalyst, but NaOH and LiOH effect mainly the Cannizzaro reaction.

Several authors have studied intermediate aldol-type condensations as part of the formose reaction sequence. Pfeil and Ruckert (12), in batch studies, showed that glycolaldehyde reacted with itself to yield hexoses and tetroses and with formaldehyde to yield C$_3$, C$_4$, C$_5$, and trace C$_6$ products. Glyceraldehyde reacted with itself and dihydroxyacetone reacted with itself to produce hexoses. Glyceraldehyde and glycolaldehyde condensed to give pentoses. Erythrose and formaldehyde also yielded pentoses. Significantly, pentoses and hexoses did not react with formaldehyde at a measurable rate. This nonreact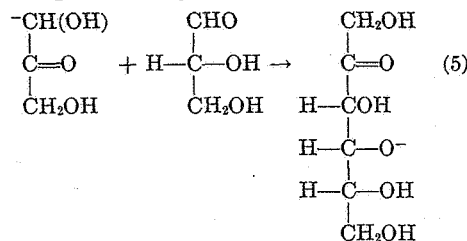ivity is probably due to formation of stable furanose and pyranose ring structures. Berl and Feazel (9) have studied in greater detail the self-condensation of glyceraldehyde in alkaline solution and the effects of dihydroxyacetone on glyceraldehyde condensation. D-Glyceraldehyde condensed with itself to give D-fructose and D-sorbose almost exclusively. Dihydroxyacetone was noted to have a catalytic effect on the glyceraldehyde condensation, while dihydroxyacetone condensed with itself to give a branched chain compound in 45% yield. Frost and Pearson (13) have discussed the mechanism of glyceraldehyde condensation. Ionization of glyceraldehyde:

$$\text{OH}^- + \text{H}\begin{array}{c}\text{CHO}\\|\\-\text{C}-\text{OH}\\|\\\text{CH}_2\text{OH}\end{array} \rightleftharpoons \begin{array}{c}\text{CHO}\\|\\^-\text{C}-\text{OH}\\|\\\text{CH}_2\text{OH}\end{array} + \text{H}_2\text{O} \quad (3)$$

is the rate determining step, followed by a proton shift to give the carbanion of dihydroxyacetone.

$$\begin{array}{c}\text{CHO}\\|\\^-\text{C}-\text{OH}\\|\\\text{CH}_2\text{OH}\end{array} \rightleftharpoons \begin{array}{c}^-\text{CH(OH)}\\|\\\text{C}=\text{O}\\|\\\text{CH}_2\text{OH}\end{array} \quad (4)$$

(These proton shifts account for the isomerization observed in the formose system.) This carbanion then reacts with glyceraldehyde to give the oxyanion of the ketohexose.

$$\begin{array}{c}^-\text{CH(OH)}\\|\\\text{C}=\text{O}\\|\\\text{CH}_2\text{OH}\end{array} + \text{H}\begin{array}{c}\text{CHO}\\|\\-\text{C}-\text{OH}\\|\\\text{CH}_2\text{OH}\end{array} \rightarrow \begin{array}{c}\text{CH}_2\text{OH}\\|\\\text{C}=\text{O}\\|\\\text{H}-\text{COH}\\|\\\text{H}-\text{C}-\text{O}^-\\|\\\text{H}-\text{C}-\text{OH}\\|\\\text{CH}_2\text{OH}\end{array} \quad (5)$$

March (14) also considers this mechanism relevant for all types of base catalyzed aldol condensations, and it has been used most recently by Gutsche et al. (7), who also report dendroketose formation.

In addition to aldol-type condensations, the Cannizzaro reaction also occurs in the formose system. The Cannizzaro reaction is the simultaneous oxidation and reduction of two aldehyde groups by hydroxyl ion. The Cannizzaro reaction of formaldehyde with Ca(OH)$_2$ has the following stoichiometry:

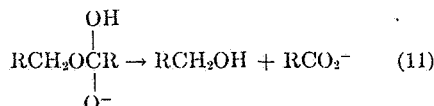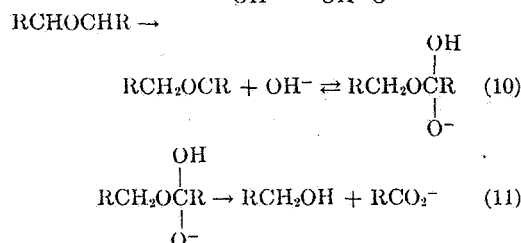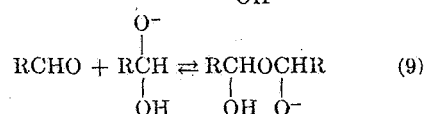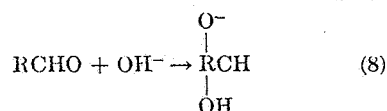$$4CH_2O + Ca(OH)_2 \rightleftharpoons (HCOO)_2Ca + 2CH_3OH \quad (6)$$
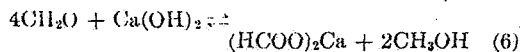
Aldose condensation products of the formose reaction can also undergo the Cannizzaro reaction, e.g., glycolaldehyde:

$$2HOCH_2CHO + OH^- \rightleftharpoons HOCH_2COO^- + HOCH_2CH_2OH \quad (7)$$
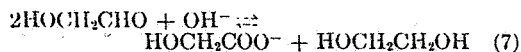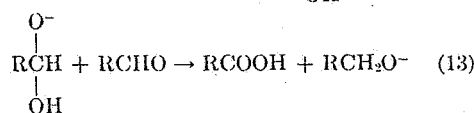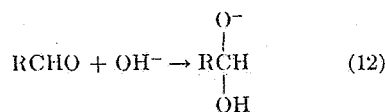
Furthermore, cross-Cannizzaro reaction may occur where two dissimilar aldehydes are oxidized and reduced. Cross Cannizzaro reaction may prove useful in reducing aldose condensation products of the formose reaction.

Several mechanisms have been proposed for the Cannizzaro reaction. Geissmann (15), in a 1944 review of Cannizzaro literature, presented the mechanism of Lock (16).

$$RCHO + OH^- \rightarrow R\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}H} \quad (8)$$

$$RCHO + R\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}H} \rightleftharpoons R\underset{\displaystyle OH}{C}HO\underset{\displaystyle O^-}{C}HR \quad (9)$$

$$RCHOCHR \rightarrow$$

$$RCH_2OCR + OH^- \rightleftharpoons RCH_2O\overset{\displaystyle OH}{\underset{\displaystyle O^-}{C}R} \quad (10)$$

$$RCH_2O\overset{\displaystyle OH}{\underset{\displaystyle O^-}{C}R} \rightarrow RCH_2OH + RCO_2^- \quad (11)$$

Geissman concluded, "This mechanism adequately coordinates the well-known variations of base-induced dismutation of aldehydes into a general picture . . ." March (14) proposed a somewhat similar mechanism,

$$RCHO + OH^- \rightarrow R\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}H} \quad (12)$$

$$R\overset{\displaystyle O^-}{\underset{\displaystyle OH}{C}H} + RCHO \rightarrow RCOOH + RCH_2O^- \quad (13)$$

again involving the singly charged methylene-glycol anion. Batch experiments conducted by Ackerlof and Mitchell (17) at 60°C show that the kinetics of the Cannizzaro reaction of formaldehyde with $Ca(OH)_2$ is

first order with respect to $Ca(OH)_2$. These studies also show that glucose is readily converted by the Cannizzaro reaction.

In summary, considering the autocatalytic nature of the exothermic formose reaction and the overall complexity of the system, the experimental approach for obtaining valid kinetics is important. A system must be thermally stable and reproducible and analytical data should be readily attainable on product composition at all conversion levels. Studies have previously been conducted in batch and plug flow reaction systems near complete conversion but not at intermediate conversion levels. The continuous stirred tank reactor (CSTR) was found in this study to be suited for both precise temperature and conversion control. A further advantage is the fact that rates are measured directly, facilitating the description of the kinetics of the system. Experiments is a CSTR by MacLean and Heinz (18) showed the feasibility of producing lower molecular weight aldoses and ketoses using lead salts as catalysts.

EQUIPMENT AND OPERATING PROCEDURES

All kinetic studies presented in this report were carried out in a CSTR. A description of the feed system, reactor, and monitoring devices follows.

The $Ca(OH)_2$ slurry and aqueous formaldehyde solution were pumped by Cole Parmer Masterflex tubing pumps through 1/32-in. and 1/16-in. Tygon tubing, respectively. The $Ca(OH)_2$ feed rate could be varied from 0 to 25 cc/min, while the formaldehyde rate could be varied from 0 to 125 cc/min. The $Ca(OH)_2$ slurry was fed from a 6-liter, magnetically stirred, Erlenmeyer flask equipped with a Drierite-Ascarite tube to prevent CO_2 contamination. Formaldehyde was fed from a 20-liter glass reagent bottle. The reaction vessel was a 300-cc, magnetically stirred, high form pyrex beaker. A combination hot plate-stirrer and a 1/8-in. stainless steel cooling loop provided a simultaneous heating-cooling ballast to the reactor. Two 200-watt quartz immersion heaters on a control circuit maintained temperature stability. The control circuit consisted of the immersion heaters on variacs

operated by a Matheson Lab Stat proportional controller. The controller sensed the mercury level in a thermometer with 0.1°C divisions. In this way temperature could be controlled to ±0.2°C. The two immersion heaters and a combination pH electrode also served as three cylindrical baffles.

The product was continuously withdrawn from the reactor by a tubing pump. The volume of fluid in the reactor could be varied by adjusting the height of the product withdrawal line. For these studies this unit was operated in the following manner:

The feed pumps were started and set to the desired control point. Feed streams were then recycled to the storage reservoirs for 30 minutes to allow the pumping rates to reach steady-state. Feed rates were then individually measured, the reactor filled, and brought to the desired temperature. A small amount of glyceraldehyde was then added to the reactor to speed attaining steady-

TABLE 1
EXPERIMENTAL DATA

Temp. (°C)	HCHO feed rate (mole/l./min)	$Ca(OH)_2$ feed rate (mole/l./min)	Residence time (min)	Concentrations in reactor (moles/l.)		
				$Ca(OH)_2$ by acid titration	HCHO by Na_2SO_3	HCHO by chromotropic acid
	0.15	0.0113	4.56	0.040	0.06	0.08
		0.0113	4.44	0.040	0.03	0.04
	0.37	0.0055	5.42	0.021	2.01	2.05
		0.0134	4.92	0.047	1.06	1.12
		0.0162	4.76	0.054	0.76	0.77
	0.35	0.0204	4.57	0.087	0.22	0.16
		0.192	5.36	0.089	0.32	0.32
		0.0272	4.24	0.113	0.09	0.09
		0.0520	4.97	0.230	Nil	0.04
		0.0715	4.75	0.300	Nil	0.04
60.0	0.78[a]	0.0130	5.37	0.047	3.99	4.13
		0.0184	5.33	0.063	3.14	3.23
		0.0356	4.94	0.133	1.65	1.70
		0.0469	4.71	0.198	0.83	0.65
		0.0585	4.60	0.252	0.30	0.32
		0.0750	4.39	0.315	0.08	0.18
	0.86	0.0138	5.57	0.047	4.70	4.73
		0.0306	4.55	0.117	2.39	2.47
		0.0516	4.20	0.187	0.95	0.96
	0.94	0.0206	5.90	0.058	5.34	5.60
		0.0448	5.43	0.155	2.22	2.22
		0.0555	5.24	0.193	1.47	1.46
		0.0872	4.74	0.360	0.15	0.13
55.0			5.74	0.127	1.78	1.93
55.0			5.91	0.130	1.75	1.83
60.0	0.52	0.0288	5.92	0.125	1.13	1.18
65.0			5.93	0.128	0.54	—
70.0			5.84	0.106	0.04	0.09

[a] CH_3OH-stabilized (Baker Analyzed Reagent, 36.9% HCHO, 12% CH_3OH). All other HCHO solutions prepared by dissolving Mallinckrodt CP paraformaldehyde. Analytical reagent grade $Ca(OH)_2$, also from Mallinckrodt, was used for all studies.

state. Actually, the reaction is self-initiating; no product addition is necessary, but a longer time period to reach steady-state is then required. The reactor was operated from ten to fifteen residence times to ensure steady-state conditions. To confirm that steady-state was attained, if duplicate consecutive HCHO measurement by Na_2SO_3 titration (after a four-residence time period) was had, it was presumed that the time allowed to reach steady-state was sufficient.

In order to be certain that the reaction was terminated, samples were taken in the following manner: A known volume of 1.00 M HCl was pipetted into a 200-cc volumetric flask. The amount of acid was always in excess of that required to neutralize the $Ca(OH)_2$ catalyst in the product. The entire product stream was then fed into the flask until full. This sample was also timed to check the flow rate out of the reactor. A portion of this acidulated sample was back-titrated until neutral to thymolphthalein (pH 9.5) by 1.00 N NaOH. This back-titration provided the basis for calculation of Cannizzaro effects; then, this same neutralized sample was used for the sodium sulfite test for formaldehyde. Another portion was adjusted to pH 4 with NaOH and freeze-dried for gas chromatography.

The remaining acidulated sample was refrigerated for later use in the chromotropic acid test for formaldehyde.

The $Ca(OH)_2$ flow rate to the reactor was then changed and measured, the reactor again was allowed to come to steady-state, and another analysis followed. In this way several experiments were performed at *constant formaldehyde feed rate* over a wide range of concentrations and formaldehyde conversions. Table 1 lists the experimental data obtained.

ANALYTICAL TECHNIQUES AND OBSERVATIONS

Formaldehyde concentrations were determined by two independent methods; the sodium sulfite and chromotropic acid tests.

The sodium sulfite test (19) is based on the reaction:

$$HCHO + Na_2SO_3 + H_2O \rightarrow NaOH + CH_2(NaSO_3)OH \quad (14)$$
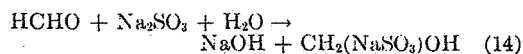
and the subsequent neutralization by HCl of the NaOH formed. The sodium sulfite test is not specific to formaldehyde, due to interference of lower molecular weight aldoses and ketoses, which are formose reaction intermediates. Table 2 shows the fractional recovery (moles of NaOH liberated/mole of aldose or ketose) measured for some aldoses and ketoses.

TABLE 2
SENSITIVITY OF Na_2SO_3 TEST TO SOME
CARBOHYDRATES

Compound	Sample size (g)	Fractional recovery
Glycolaldehyde	1.17	0.95
Glyceraldehyde	1.52	0.94
	0.43	0.86
Dihydroxyacetone	1.18	0.34
D-Arabinose	3.06	0.217
Fructose	3.17	0.014
Dextrose monohydrate	3.32	0.032

Chromotropic acid (4,5-dihydroxynaphthalene-2,7-disulfonic acid) reacts with formaldehyde in the presence of concentrated sulfuric acid at elevated temperatures to give a characteristic violet color, which can be monitored colorimetrically at 570 mμ. The procedure of Bricker and Johnson (20) was slightly modified by consistently using a 10-μl aqueous sample whose formaldehyde molarity was between 0.03 to 0.11. Results specific for HCHO only were reproducible to within 0.5% of a full scale colorimeter reading. A comparison of the product analyses obtained by the sodium sulfite and chromotropic acid tests is shown in Fig. 1 to be independent of HCHO concentration, over the range studied. When the conversion level of formaldehyde calculated from the results of the two tests is compared, results are identical to within experimental error. Near HCHO conversion levels of 95% (i.e., very low HCHO concentration), some interference with the chromotropic acid test was noted by a rose color instead of the characteristic violet color. Figure 2 shows parameters of reaction selectivity to glycolaldehyde on a plot comparing conversions by
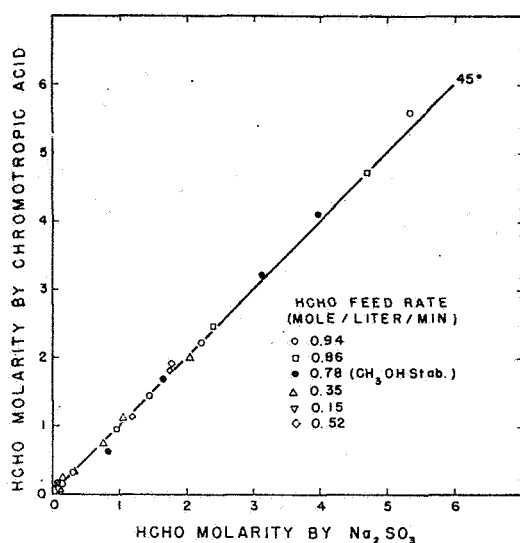
FIG. 1. Agreement in HCHO analyses of 60°C formose products over the entire range of concentrations studied.

FIG. 2. Agreement in HCHO analyses of 60°C formose products at various conversion levels indicates that concentrations of intermediates are minimal.

the two methods. The agreement of the two tests is an indication that selectivity of the formose reaction to lower molecular weight aldoses and ketoses is minimal under the conditions used in this experimental study.

In order to analyze product distributions, volatile trimethyl silyl (TMS) ether derivatives of pH 4 freeze-dried reaction products were prepared, using Sweeley's procedure (21). This involves reacting a two to one volumetric mixture of hexamethyldisilazane (HMDS) and trimethylcholorosilane (TMCS) with the dry sample dissolved in pyridine.

A 50-foot Perkin-Elmer Support Coated Open Tubular (SCOT) column with OV-17 methyl phenyl silicone gum liquid phase, as described by Averill (22), was used for separation of the TMS derivatives. Analyses were made using both Model 800 and Model 900 Perkin-Elmer gas chromatographs. The injector and flame ionization detector were maintained at 220°C, and column temperature was programmed linearly at 4°C/min from 100° to 240°C. Nitrogen carrier gas was used at 4 cc/min STP.

Experiments where a mixture of ethylene glycol, glycerol, erythritol, arabitol, and mannitol were dissolved in pyridine and
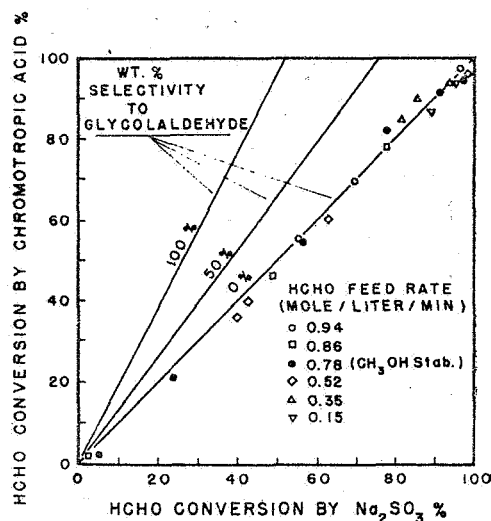
silylated show that the flame ionization detector gave a constant response (peak area/gm of parent compound) for all the TMS ethers to within ±10%. Table 3 is a comparison of relative retention time data obtained in this study, Sweeley's results on an Se-52. column at 140°C, and Averill's results on the OV-17 column (linear temperature program 150°–200°C at 2.5°C/min). Dihydroxyacetone and glyceraldehyde are mainly present as dimers. Mixtures of carbohydrate reference samples enabled relative retention times to be established. The absolute retention time for β-glucose was 29.6 ± 0.5 minutes.

Carbohydrate reference samples were also reduced to polyols by $NaBH_4$ using Sweeley's procedure (except that borates were removed by adding large quantities of methanol to the reduced sample and drying on a rotary evaporator). The reduced samples were then silylated and analyzed in the same manner as the nonreduced samples. A mixture of glyceraldehyde, dihydroxyacetone, erythrose, arabinose, ribose, xylose, fructose, galactose, glucose, and mannose was reduced and analyzed. The analysis showed that the reduction of polyols was completely quantitative, in that relative areas corre-

TABLE 3
Relative Retention Times for TMS Derivatives

Parent compound	Relative retention time		
	OV-17 (Weiss et al.), 100°–240°C at 4°C/min	OV-17 (Averill), 150°–200°C at 2.5°C/min	SE-52 (Sweeley), 140°C
Ethylene glycol	0.118	—	—
Glycerol	0.297	—	—
Glycolaldehyde	0.355(s)	—	0.039[a](s)
Glycolaldehyde	0.370	—	0.044
Glycolaldehyde	0.388(s)	—	—[b]
Erythrose	0.477	—	0.10
Erythrose	0.490	—	0.12
Erythrose	—[b]	—	0.14
Erythritol	0.510	—	0.16
Dihydroxyacetone	0.574	—	—[b]
Arabinose	0.666	0.43	0.28
Lyxose	0.666	—	0.26
Ribose	0.689	0.47	0.27(s)
Ribose	0.697(s)	0.48	0.32
Arabinose	0.708	—[b]	0.33
Lyxose	0.708	—	0.33
Ribose	0.715	0.50(s)	0.35
Arabitol	0.737	—	0.46
Xylitol	0.737	—	0.42
Ribitol	0.737	—	0.46
Xylose	0.765	0.58	0.43
Xylose	0.813	—[b]	0.54
Dihydroxyacetone	0.813	—	0.57
β-Fructose	0.823	0.67	0.69
Mannose	0.836	0.70	0.70
Fructose	0.836	—	—[b]
Galactose	0.864(s)	—[b]	0.076(s)
Glyceraldehyde	0.868	—	0.48
Sorbose	0.894	0.80	0.85
Galactose	0.894	0.80	0.88
Mannitol	0.909	—	1.21
Mannose	0.914	0.84(s)	1.08(s)
Dulcitol	0.922	—	1.28
Sorbitol	0.922	—	1.24
Galactose	0.928	—[b]	1.08
α-Glucose	0.928	0.86	1.00
β-Glucose	1.000	1.000	1.57

[a] Sweeley claims this peak is glyceraldehyde monomer.

[b] No peak observed.

(s) = Minor component.

sponded to the relative amounts of material that was reduced. It is possible that significant losses of ethylene glycol can result from the evaporation step.

All reaction products produced in the CSTR were analyzed in both the reduced and nonreduced forms. Chromatograms for the series of experiments at 0.35 mole/liter/min HCHO feed rate and at 60°C are shown on Fig. 3 in order of increasing Ca(OH)$_2$ concentration (i.e., reaction severity and, hence, conversion). The complexity of the

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unreduced products (light lines) relative to the reduced products (heavy lines) is evident. Ethylene glycol is not shown.

Formaldehyde conversion level has a definite effect on product distribution. Most evident is the fact that the product obtained at complete conversion is markedly different than that obtained at intermediate conversion levels. Attempts to identify the major components of the unreduced mixture have been unsuccessful to date. Since low molecular weight compounds form dimers readily, analyses of unreduced products give a misleading picture of molecular weight distribution of the formose.

The chromatograms of reduced products do provide information on carbon number groupings for C_3 and higher products. Glycerol is the only C_3 material present. Erythritol is the major C_4 component at high conversion levels. The C_4 material dominant at low conversions is unidentified; and it may either be threitol or a branched chain compound. The major C_5 compounds at high conversions correspond to xylitol, ribitol, and arabitol, which are not separated in this analysis. At low conversion, the major C_5 component is unknown. Mannitol and dulcitol and/or sorbitol are apparently present in small proportions in the C_6 fraction, but the major C_6 polyols are unidentified. Higher molecular weight unidentified material is also produced in the formose reaction.
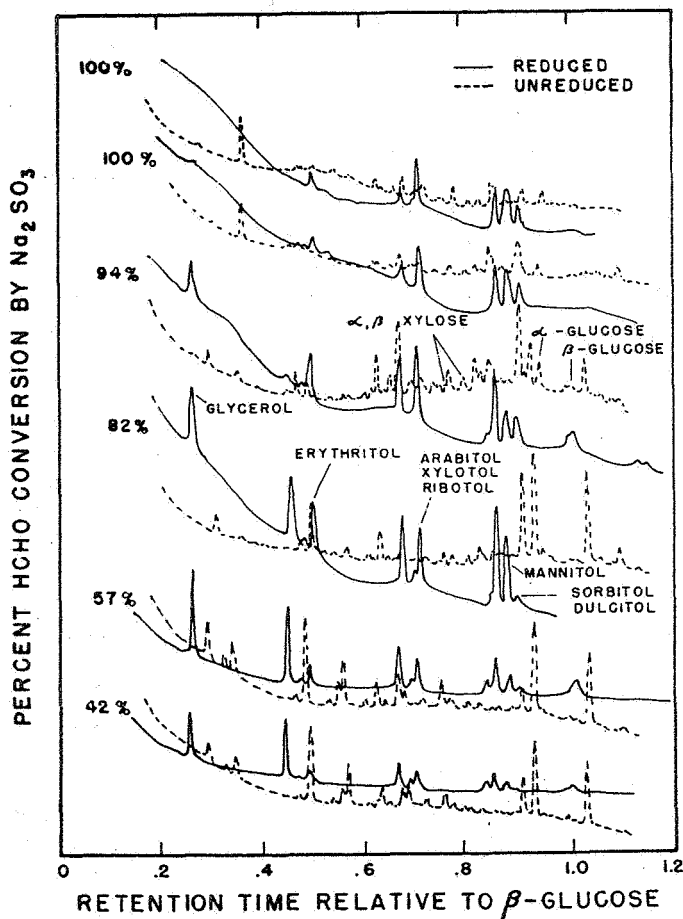
Fig. 4 shows the distribution by carbon

FIG. 3. Formose chromatograms before (light lines) and after (heavy lines) reduction. 60°C products at varing coversion levels, 0.35–0.37 moles HCHO/liter/min.

number of the C_3 and higher species pro-
duced in the formose reaction at 60°C as
a function of formaldehyde conversion.
Weight percents are regarded as identical to
area percents of the reduced chromatograms.
No parameters of formaldehyde feed rate
are apparent. C_3 and C_4 compounds pre-

dominate at low conversion levels; at com-
plete conversion, the terminal products are
10% C_4, 30% C_5, 55% C_6, and 5% > C_6. The
GLC analyses also confirm the earlier conclu-
sion that there is little selectivity to lower
molecular weight species at the conditions
studied.
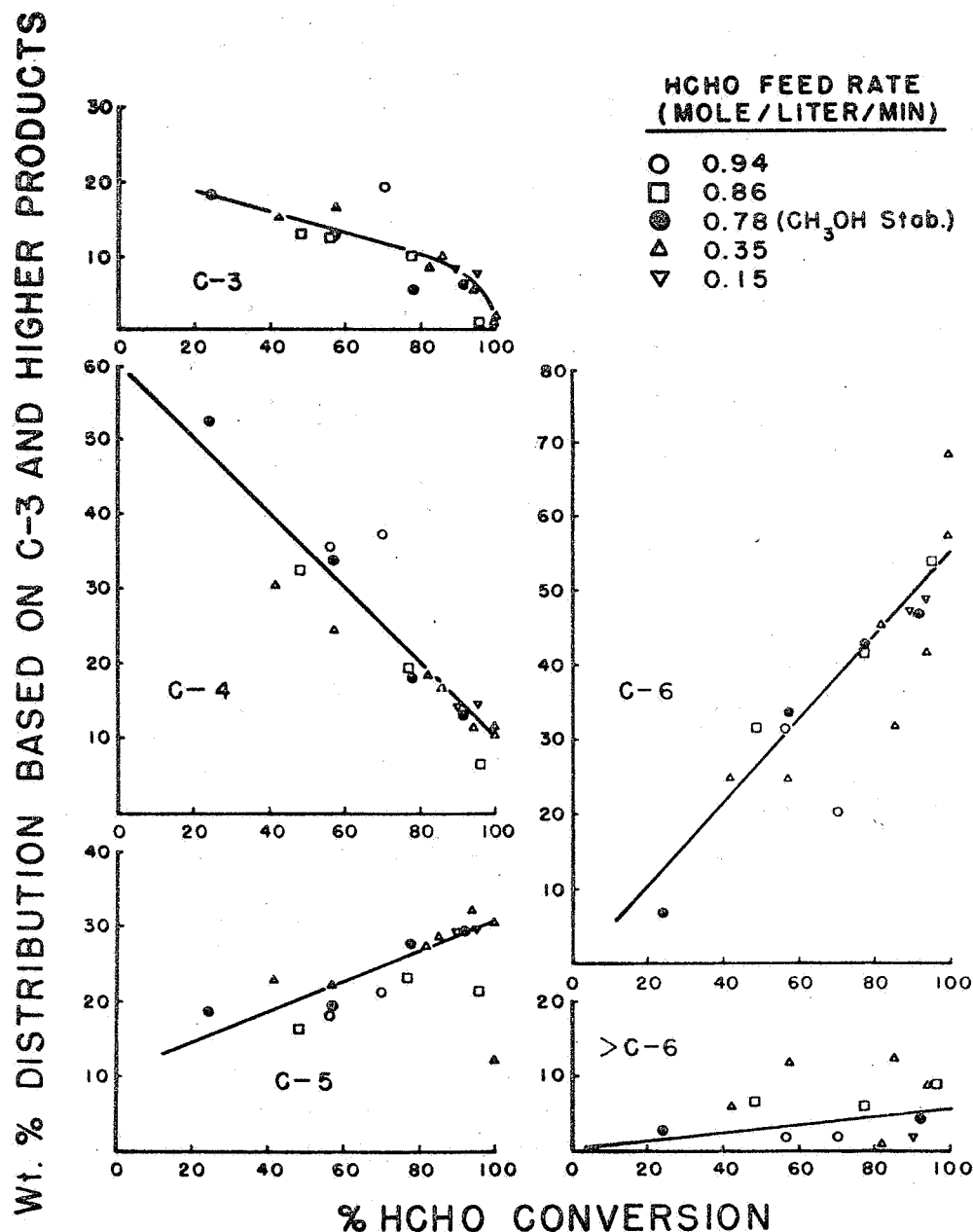
Fig. 4. Distribution of formose C_3 and higher products at 60°C (HCHO feed rates noted).

EXPERIMENTAL RATE CORRELATIONS

In the series of experiments to determine the effect of formaldehyde and calcium hydroxide concentrations on reaction rate, the formaldehyde feed rate was held constant while $Ca(OH)_2$ feed rate was altered. By this means, products were produced over the complete formaldehyde conversion range. Fig. 5 shows the formaldehyde reaction rate
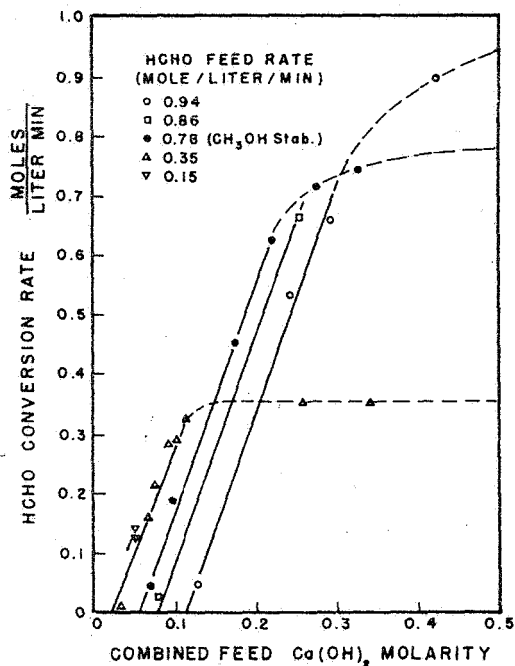
FIG. 5. Total formaldehyde conversion rate at 60°C vs. total calcium present in system. Note parameters of HCHO feed rate.

as a function of total calcium molarity at 60°C. The data fit a series of parallel straight lines with parameters of formaldehyde feed rate. Of course, at very high conversion, reaction rate approximates feed rate, and linearity is lost. Fig. 5 shows that an increase in formaldehyde feed rate decreases the reaction rate at any given total calcium molarity. This apparent negative order functionality in formaldehyde is due to Cannizzaro reaction of the $Ca(OH)_2$ catalyst. In some cases, as much as 50% of the $Ca(OH)_2$ was reacted, and so, calcium salts that are not $Ca(OH)_2$ and therefore not

catalysts are included in a measurement of the total calcium hydroxide fed to the reactor.
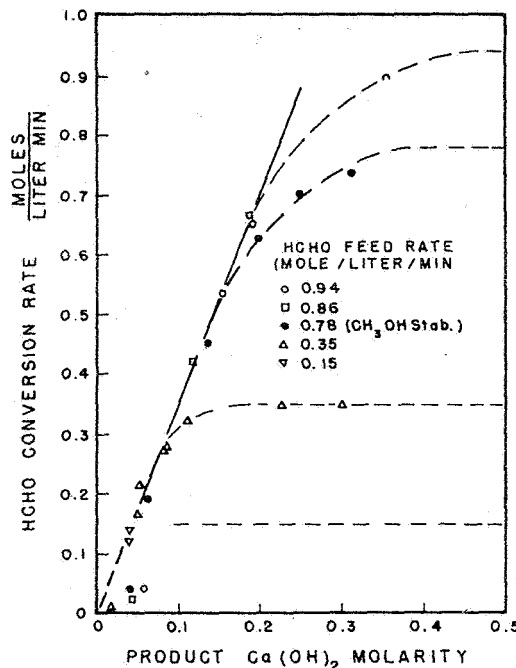
Figure 6, a plot of formaldehyde reaction

FIG. 6. Total formaldehyde conversion rate at 60°C is independent of organic species concentration at intermediate conversion levels when plotted against $Ca(OH)_2$ concentration rather than total calcium concentration (HCHO feed rates noted).

rate vs. $Ca(OH)_2$ concentration in the reactor (rather than its concentration in the combined feed), as determined by acid titration of the product, eliminated the parameters of formaldehyde feed rate at intermediate conversion levels. At these conversion levels, formaldehyde reaction rate is first order in $Ca(OH)_2$ and zero order in formaldehyde and product concentrations, or

formaldehyde reaction

$$\text{rate} = k\ Ca(OH)_2, \quad (15)$$

where $k = 3.5(min^{-1})$ at 60°C.

In order to eliminate Cannizzaro effects from the formaldehyde reaction rate data, formose reaction rate r_F was defined as [formaldehyde reaction rate $-4 \times Ca(OH)_2$ reaction rate], as determined by the stoichiometry of the Cannizzaro reaction [see
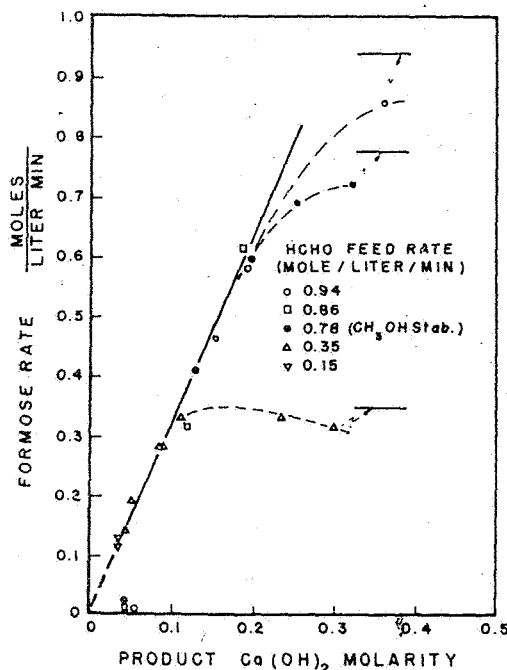
Fig. 7. Formose reaction rate (i.e., condensation reactions only) is zero order in organics and first order in $Ca(OH)_2$ at 60°C at intermediate conversion levels.

Reaction (6)]. Fig. 7 records the formose reaction rate as a function of $Ca(OH)_2$ product molarity. One line, independent of HCHO concentration in the reactor, fits intermediate conversion level data. Note that this line passes through the origin. Schmalfuss (23), in a study of the MgO-catalyzed for-

maldehyde condensation, observed similar behavior, almost independent of HCHO concentrations and first order in MgO which had not been consumed in the Cannizzaro reaction. A zero order rate constant can be calculated from the slope of this straight line. For the formose reaction at 60°C the slope is 3.15 (min⁻¹) [moles HCHO/liter]/ [moles $Ca(OH)_2$/liter]. A comparison of Figs. 6 and 7 shows that formaldehyde disappears mainly by Cannizzaro reaction at low conversion levels.

Thus, at intermediate conversion levels, for the conditions studied, the formose reaction rate is zero order in organics and first order in calcium hydroxide:

r_F = formose reaction
$$\text{rate} = k_F\, Ca(OH)_2, \quad (16)$$

where $k_F = 3.5$ (min⁻¹) at 60°.

These investigations have also confirmed that the formose reaction is autocatalytic. Figure 8, a plot of formose rate divided by $Ca(OH)_2$ concentration vs. formaldehyde molarity in the reactor, shows that this normalized rate passes through a maximum at intermediate conversion levels, as predicted by an autocatalytic rate law.

One series of experiments was carried out, at constant formaldehyde and $Ca(OH)_2$ feed rates while temperature was varied, to determine the activation energy of the formose reaction. This series gave a set of reaction rate data which was lower than expected when compared to the rest of the experi-
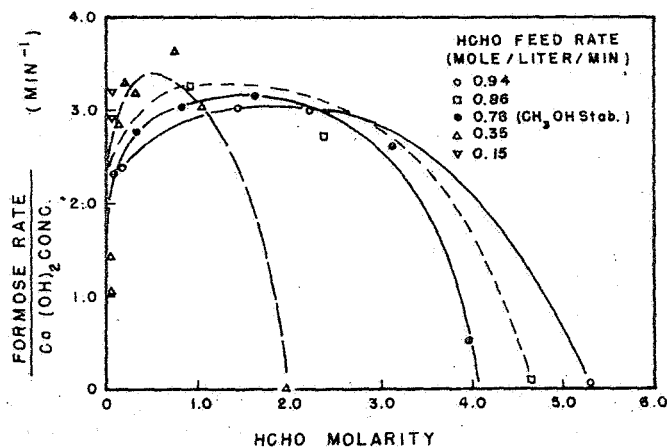

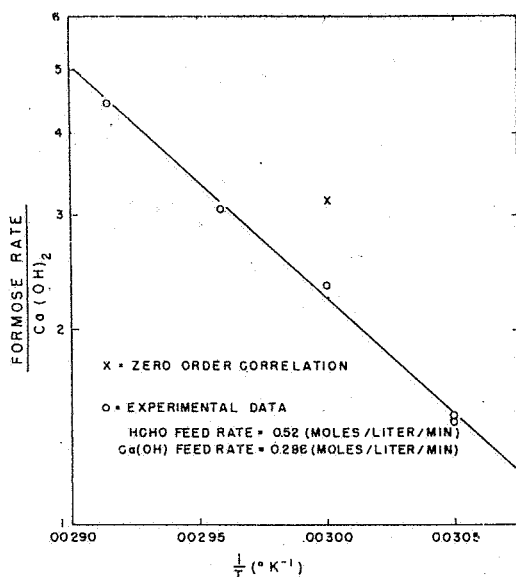Fig. 8. The autocatalytic behavior of the formose reaction at 60°C.

Fig. 9. Arrhenius plot for the formose reaction at intermediate conversion levels; k = formose rate/Ca(OH)$_2$ E = 16,000 cal/gm mole.

mental data. The data do, however, show internal consistency. Figure 9 is an Arrhenius plot of these data, which yielded an activation energy of 16 kcal/mole. The point (X) represents the previously mentioned 60°C zero order rate constant value of 3.15.
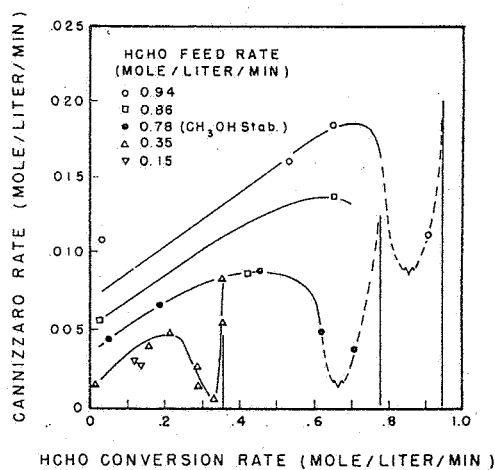
A study of the Cannizzaro effects in the

Fig. 10. The relationship between Cannizzaro rate and total HCHO conversion rate at 60°C. HCHO feed rates indicated.

formose reaction shows that these effects are dependent on formaldehyde conversion level. Figure 10, a plot of Cannizzaro rate vs. formaldehyde conversion rate with parameters of formaldehyde feed rate, shows that Cannizzaro rate passes through a maximum at intermediate conversion levels, then a minimum at higher levels, and finally increases sharply above 95% conversion. Figure 11 is a plot of ln (Cannizzaro rate/Ca(OH)$_2$ concentration) vs. ln (formaldehyde concentration) taken from both low conversion data in the CSTR and from Ackerlof and Mitchell's batch data at the same 60°C temperature. The line drawn on Fig. 11 corresponds to a slope of unity. An approximate first order dependency of the Cannizzaro reaction rate of formaldehyde concentration, as well as agreement of the present CSTR data with earlier batch data, are shown on Fig. 11.
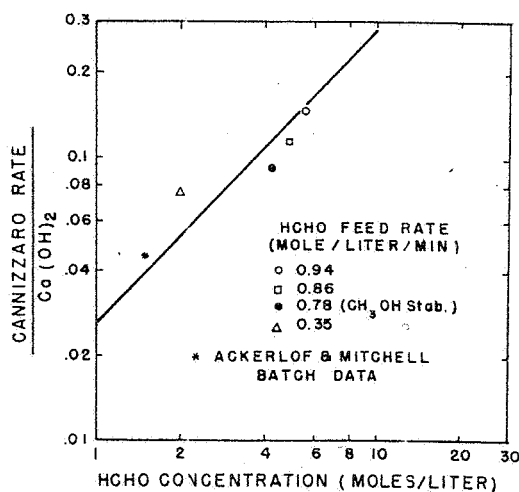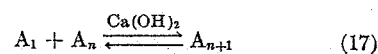

Fig. 11. Cannizzaro rate below 10% conversion is first order in both Ca(OH)$_2$ and HCHO at 60°C. Line drawn has slope of unity.

The Ca(OH)$_2$ catalyzed condensation of formaldehyde (A$_1$) with condensation product A$_n$ of carbon number n to produce a product A$_{n+1}$ one carbon number higher can be written

$$A_1 + A_n \xrightleftharpoons{Ca(OH)_2} A_{n+1} \qquad (17)$$

with equilibrium constant

$$K = \frac{A^e_{n+1}}{A_1^e A_n^e} \qquad (18)$$

where superscript e denotes the concentration at equilibrium. Consider this overall reaction as resulting from four independent kinetic steps.

analogy to Langmuir-Hinshelwood type rate expressions except for a difference in semantics—complexing-decomplexing is substituted for adsorption-desorption. Expressions for the net rate of the overall reaction have been developed for each of these kinetic

Step No.	Molecular process	Description
1	$A_1 + Ca(OH)_2 \rightleftharpoons A^*_1$	complexing-decomplexing of formaldehyde with Ca(OH)$_2$ (19)
2	$A_n + Ca(OH)_2 \rightleftharpoons A^*_n$	complexing-decomplexing of A_n with Ca(OH)$_2$ (20)
3	$A^*_n + A^*_1 \rightleftharpoons A^*_{n+1} + Ca(OH)_2$	reaction of complexed species (21)
4	$A^*_{n+1} \rightleftharpoons A_{n+1} + Ca(OH)_2$	decomplexing-complexing of product A_{n+1} (22)

where A^*_n represents the complexed form of A_n with Ca(OH)$_2$.

Furthermore, define S as the total number of active sites where:

$$S = Ca(OH)_2 + \sum_1^{n+1} A^*_n \qquad (23)$$

$$= \text{uncomplexed } Ca(OH)_2$$
$$+ \text{ complexed organics} \qquad (24)$$

$$= \text{total } Ca(OH)_2 \text{ as determined by}$$
$$\text{acid titration of the product.} \qquad (25)$$

The rate expression and equilibrium constant for each of these steps follow, where $\theta_{A^*_n}$ is the fraction of active sites complexed by A_n.

steps, assuming that particular step is rate limiting (24, 25). Experimentally it has been shown (4, 5) that formaldehyde and condensation products such as glycolaldehyde, glyceraldehyde, etc., are readily complexed; there is no indication that steps 1 and 2 are rate limiting. The relatively low activation energy of 16 kcal/mole might suggest, but certainly does not prove, that step 3, the condensation reaction itself, is not rate limiting. More important, there is no means of rationalizing zero order behavior from the rate expression that can be derived from step 3 limiting.

Assume that step 4, the decomplexing reaction, is rate limiting

| Step No.	Rate expression	Equilibrium constant
1	$r_1 = \overrightarrow{k_1}A_1(1 - \theta_{A^*_1} - \theta_{A^*_n} - \theta_{A^*_{n+1}})S - \overleftarrow{k_1}\theta_{A^*_1}S$	$K_1 = \dfrac{\overrightarrow{k_1}}{\overleftarrow{k_1}}$ (26)
2	$r_2 = \overrightarrow{k_2}A_n(1 - \theta_{A^*_1} - \theta_{A^*_n} - {A^*_{n+1}})S - \overleftarrow{k_2}\theta_{A^*_n}S$	$K_2 = \dfrac{\overrightarrow{k_2}}{\overleftarrow{k_2}}$ (27)
3	$r_3 = \overrightarrow{k_3}\theta_{A^*_n}\theta_{A^*_1}S^2 - \overleftarrow{k_3}\theta_{A^*_{n+1}}(1 - \theta_{A^*_1} - \theta_{A^*_n} - \theta_{A^*_{n+1}})S^2$	$K_3 = \dfrac{\overrightarrow{k_3}}{\overleftarrow{k_3}}$ (28)
4	$r_4 = \overrightarrow{k_4}\theta_{A^*_{n+1}}S - \overleftarrow{k_4}\theta_{A^*_{n+1}}(1 - \theta_{A^*_1} - \theta_{A^*_n} - \theta_{A^*_{n+1}})S^2$	$K_4 = \dfrac{\overrightarrow{k_4}}{\overleftarrow{k_4}}$ (29)

The overall equilibrium constant for this sequence becomes

$$K = \frac{A^e_{n+1}}{A_1^e A_n^e} = K_1K_2K_3K_4. \qquad (30)$$

Note that this scheme is in accord with the reaction mechanism proposed by Frazen and Hauck (see Equation 2). These relationships are obviously nothing more than a direct

$$r_F = \frac{k_4K_1K_2K_3S\left[A_1A_n - \dfrac{1}{K}A_{n+1}\right]}{1 + K_1A_1 + K_2A_n + K_1K_2K_3A_1A_n}. \qquad (31)$$

Since complexing takes place so readily, $K_1 \gg 1$ and $K_2 \gg 1$. It has been shown by us and also other investigators (7, 8) that the formose reaction is effectively undirectional:

$$A_1 + A_n \rightarrow A_{n+1} \qquad (32)$$
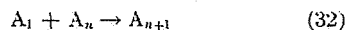
and therefore $K_3 \gg 1$.

Neglecting the reverse reaction (which would only be important at extremely high conversion levels), Equation 32 reduces to

$$r = \frac{\overleftarrow{k_4} K_1 K_2 K_3 S A_1 A_n}{K_1 A_1 + K_2 A_n + K_1 K_2 K_3 A_1 A_n}. \qquad (33)$$

At low conversion levels where $A_1 > A_n$, then

$$K_1 A_1 > K_2 A_n$$

and

$$K_1 A_1 > K_1 K_2 K_3 A_1 A_n,$$

and

$$r = \overleftarrow{k_4} K_2 K_3 S A_n, \qquad (34)$$

which implies autocatalytic behavior (i.e., at low conversion, rate depends on the concentration of intermediates). Furthermore, at intermediate conversion levels, since $K_1 K_2 K_3 > 1$, the $K_1 K_2 K_3 A_1 A_n$ term in the denominator of the rate expression will predominate and the rate expression becomes

$$r = \overleftarrow{k_4} S, \qquad (35)$$

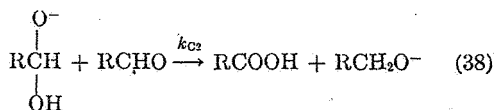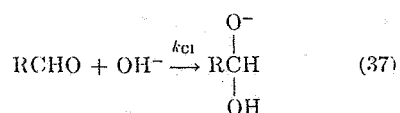zero order in product and formaldehyde. This was indeed experimentally observed; and the value of $\overleftarrow{k_4}$ is 3.15 min^{-1}. At high conversion, a first order relationship can be predicted, since $K_2 A_n$ will be the predominant term.

$$r = \overleftarrow{k_4} K_1 K_3 S A_1. \qquad (36)$$

We have not tested this experimentally.

Not only the behavior of the formose reaction, but also the behavior of the Cannizzaro reaction can be accounted for.

At low formaldehyde conversion levels, the first order dependency of the Cannizzaro reaction on formaldehyde and Ca(OH)$_2$ can be explained as follows: Consider March's (14) mechanism for the Cannizzaro reaction

$$\text{RCHO} + \text{OH}^- \xrightarrow{k_{C1}} \underset{\underset{\text{OH}}{|}}{\overset{\overset{\text{O}^-}{|}}{\text{RCH}}} \qquad (37)$$

$$\underset{\underset{\text{OH}}{|}}{\overset{\overset{\text{O}^-}{|}}{\text{RCH}}} + \text{RCHO} \xrightarrow{k_{C2}} \text{RCOOH} + \text{RCH}_2\text{O}^- \qquad (38)$$

which has the following rate expression

$$-r_C = k_{C1}(\text{RCHO})(\text{OH}^-) + k_{C2}(\underset{\underset{\text{OH}}{|}}{\overset{\overset{\text{O}^-}{|}}{\text{RCH}}})(\text{RCHO}) =$$
$$k_{C1}(\text{RCHO})(\text{OH}^-) + k_{C2}(\text{I})(\text{RCHO}), \qquad (39)$$

where $-r_C$ = the rate of aldehyde conversion by the Cannizzaro reaction. A steady state approximation on the intermediate anion, I, whose rate of production = r_I, is

$$r_I = k_{C1}(\text{RCHO})(\text{OH}^-) - k_{C2}(\text{I})(\text{RCHO}) = 0 \qquad (40)$$

or

$$(\text{I}) = \frac{k_{C1}}{k_{C2}}(\text{OH})^-. \qquad (41)$$

Substitution of the value of I reduces the Cannizzaro rate expression for aldehyde conversion to

$$-r_C = 2k_{C1}(\text{RCHO})(\text{OH})^-. \qquad (42)$$

The maximum in the Cannizzaro rate at intermediate conversion levels will now be derived. Rewrite the Cannizzaro rate expression for formaldehyde conversion:

$$-r_C = k_C A_1 Ca(\text{OH})_2, \text{ where } k_C = 2k_{C1}, \qquad (43)$$

and the rate expression for the formose reaction [see Equation (35)]:

$$r_F = \overleftarrow{k_4} Ca(\text{OH})_2 = \frac{A_1{}^0 - A_1}{\tau}, \qquad (44)$$

where $A_1{}^0$ is the combined feed formaldehyde concentration into the reactor and τ is the residence time. Since, at intermediate conversion levels for the reactions studied, $r_F \gg r_C$,

$$\frac{A_1 - A_1{}^0}{\tau} = \overleftarrow{k_4} Ca(\text{OH})_2. \qquad (45)$$

That is, total formaldehyde disappearance can be approximated by the formose rate alone. Furthermore, define fractional conversion x such that

$$A_1 = A_1{}^0(1 - x); \qquad (46)$$

then

$$Ca(OH)_2 = \frac{A_1^0 x}{\overleftarrow{k_4}\tau}, \qquad (47)$$

Substituting these values into Equation (43), the expression for the Cannizzaro reaction rate, we obtain

$$r_C = k_C A_1^0 (1 - x) \frac{A_1^0 x}{\overleftarrow{k_4}\tau} (1 - 2x). \qquad (48)$$

Differentiation gives

$$\frac{dr_C}{dx} = \frac{k_C (A_1^0)^2}{\overleftarrow{k_4}\tau} (1 - 2x) \qquad (49)$$

Where the differential of the rate equals zero, we find that the maximum Cannizzaro rate will occur at 50% conversion. Admittedly, this is an oversimplified approach, for other aldehydes in the system may also undergo Cannizzaro reaction, but it does qualitatively account for the observed behavior of Cannizzaro reaction passing through a maximum at intermediate conversion levels.

At extreme conversion levels, e.g., 95%, where operating conditions are forced, Cannizzaro reaction of products becomes excessive, and the Cannizzaro rate, which has previously passed through a maximum, will go through a minimum and proceed to increase again.

Conclusions

Combined feed concentrations of formaldehyde and $Ca(OH)_2$ ranged from 0.65 to 5.60 and from 0.030 to 0.340 M, respectively, with residence times typically 4 to 5 minutes. The temperature of the kinetic study was fixed at 60°C. Investigations at other temperatures and concentrations are continuing. This particular reaction is so complex that it should be expected to observed transitions to different behavior (particularly with respect to the relative magnitudes of the formose and Cannizzaro reactions and to the apparent zero order behavior at intermediate conversion levels) at conditions other than used here. In the present study, the concentration levels of intermediates were minimal.

The most serious approximation made to develop the mechanism was to describe the reaction intermediates and products as one species each, A_n and A_{n+1}. Undoubtedly, the formose reaction is a complex network whose overall behavior is a function of the concentrations of many individual species. In fact, the formose product might be regarded as the carbohydrate analog of petroleum, in that it contains so many carbohydrates of varying molecular weight and isomeric structure.

The utility of the continuous stirred tank reactor in this study should not be underestimated. Neither reaction rate measurements nor samples of formose products at intermediate conversion levels have been reported before. In this respect, use of the CSTR should be considered whenever a homogeneously catalyzed reaction exhibits an induction period in batch studies.

We have shown that the reaction of formaldehyde with $Ca(OH)_2$ in a homogeneous aqueous system proceeds by two paths, both first order in $Ca(OH)_2$: One path is first order in formaldehyde, producing Cannizzaro products. The other path, producing formose condensation products, is autocatalytic at low conversion levels and independent of the concentration levels of organic reactants and products at intermediate conversion levels. The zero order formose behavior requires that Cannizzaro rate pass through a maximum at intermediate conversion levels. This was indeed observed.

The semantic analogy of "complexing-decomplexing" in homogeneous systems to "adsorption-desorption" in heterogeneous systems provided a tool for explaining both the autocatalytic nature of the formose reaction and the zero order behavior at intermediate conversion level. It was postulated that HCHO, intermediates, and products underwent complexing-decomplexing reactions, and that reaction took place between complexed HCHO and complexed intermediate. Complexing-decomplexing can actually be visually observed [e.g., one can watch $Ca(OH)_2$ dissolve well past its 60°C solubility limit of 0.016 M]. The reaction step proposed is in accord with mechanisms proposed by earlier investigators, but it is shown here that not the reaction step, but

rather, product decomplexing, is the rate-limiting step of the formose reaction. Other mechanisms were tested, such as coordination of two species on a single calcium center, but it has not yet been possible to rationalize all observed phenomena with a model other than the one chosen.

These analogies to Langmuir-Hinshelwood relationships could be used to correlate other homogeneously catalyzed reactions. It is not unreasonable to expect that some of the many other homogeneously catalyzed reactions that have an induction period are actually reactions in which product decomplexing is the rate-controlling step.

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